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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/828,423	04/05/2001	Jennifer L. Hillman	PF-0505-2-DIV	6586

27904 7590 03/11/2003

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EXAMINER	
DECLOUX, AMY M	

ART UNIT	PAPER NUMBER
1644	12

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/828,423	HILLMAN ET AL.	
	Examiner	Art Unit	
	Amy M. DeCloux	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-21* is/are pending in the application.

4a) Of the above claim(s) *4,7,9,10,13,18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,5,6,8,11,12,14-17,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendment and declaration, filed 11-25-02 as Papers No. 10 and 11, respectively, are acknowledged and have been entered.

The declaration under 37 CFR 1.132 filed 11-25-02 (Paper No. 11) is insufficient to overcome the rejection of claims 3, 5-6, 8 and 11-12 and 14-17, based upon the rejections as set forth in the last Office action, because of the following reasons outlined in the response to Applicant's traversals of the outstanding rejections below.

MAINTAINED Claims 3, 5-6, 8, 11-12, 14-17, and newly added claims 20-21, are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility, a credible asserted utility or a well-established utility.

MAINTAINED Claims 3, 5-6, 8, 11-12, 14-17, and newly added claims 20-21, are also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by a either a specific and substantial asserted utility, a credible asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicant traverses the rejections on the grounds that as demonstrated by the Furness Declaration filed 11-25-02, the person of ordinary skill in the art can achieve beneficial results from the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds in the absence of any knowledge as to the precise function of the protein, by the use of the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds for gene expression monitoring applications including toxicology testing, said uses being independent of its precise function. However, the examiner notes that this is not a specific utility as required by the statute.

The examiner acknowledges that the description of the Figures in the instant application states that SEQ ID NO:1 is the amino acid sequence of GAPIP and that SEQ ID NO:2 is the nucleic acid sequence of GAPIP.

Applicant contends that the similarity of the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds to another protein of undisputed utility (human pre-inter-a-trypsin inhibitor) demonstrates the utility of the GAPIP, and there is a substantial likelihood that GAPIP is similarly useful. Applicant contends that given that the SEQ ID NO:1 polypeptide to which the claimed antibody binds shares more than 40% sequence identity over 70 amino acid residues with human pre-inter-a-trypsin inhibitor, there is more than enough homology to demonstrate a reasonable probability that the utility of human pre-inter-a-trypsin inhibitor can be imputed to the polypeptide of the claimed invention. Applicant supports said contention by citing Brenner (PNAS 95:6073-78) (1998) who says that it is well known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acids is exceedingly small. However, the examiner notes that relatedness does not correlate to functional identity.

From the examiner's reading of said paper by Brenner, pairwise sequence comparison methods (ie BLAST, FASTA) were assessed using a set of proteins whose relationship are known reliably from their structures and functions as described in the Structural Classification of Proteins (SCOP) database (see first line of the Abstract). The SCOP database provides a uniquely reliable set of known homologs which were identified structurally, independently of sequence comparisons, (see page 6073, column 2, fourth full paragraph, and page 6074, column 2, last sentence of fourth full paragraph). From the SCOP database, Brenner et al extracted the sequences of domains of proteins, and created two databases: 1) Database PDP90D-B, which has domains which were all less than 90% identical to each other, and 2) database PDP40D-B, which has domains which were all less than 40% identical to each other (see page 6074, column 2, second full paragraph). Brenner et al disclose that the PDP40D-B database focuses on distantly related domains (see page 6074, column 2, first two lines of the third full paragraph).

The instant specification fails to provide sufficient objective evidence of any activity for the claimed antibody and the SEQ ID NO:1 polypeptide to which the antibody specifically binds. A disclosure of sequence identity between two polypeptide by itself does not give the skilled artisan the ability to assign overlapping functions to said polypeptide, as evidenced by Skolnick et al (Trends in Biotech. 18(1):34-39, 2000) who teach that assigning functional activities for any protein based upon sequence homology is inaccurate, in part because of the multi-functional nature of polypeptide (see entire article, including the Abstract and page 34).

It is noted that Wilson et al (Current Opinion in Immunology 1998, 10(1):67-73) disclose in the Abstract that homologs of MHC molecules have diverse roles ranging from regulation of iron metabolism by the hemochromatosis gene product (HFE, a.k.a HH), to antigen presentation by CD1. Therefore it is clear that structural homology among family members does not necessarily predicate identical functions, as evidenced in more detail by US Patent 6,140,305. '305 teaches that HH shows a high degree of homology with antigen presenting MHC Class I proteins at the amino acid level through out all four domains (the peptide binding domain, the immunoglobulin like domain, the transmembrane region and the small cytoplasmic domain), and contains similar hydrophilicity, surface probability, and secondary structure which includes the conserved feature of several intradomain disulfide bonds which function in protein folding, and the ability to interact with beta-2 microglobulin (see entire patent, especially column 22, lines 1-65). Therefore, said MHC class I homologs, which are members of the immunoglobulin family, display a wide range of functions and yet would yield statistically significant scores when analyzed with the algorithms taught by Brenner et al. See the attached alignment of the hemochromatosis gene product with a human MHC Class I antigen which yielded an E value of 10-42.

Applicant further contends that the uses of the claimed antibody and the SEQ ID NO:1 polypeptide to which the antibody specifically binds for toxicology testing, drug discovery and disease diagnosis re practical uses that confer specific benefits to the public. The Examiner does not necessarily disagree that specific benefits to the public can be realized using the claimed antibody; however, said specific benefits of do not confer a specific utility to the claimed antibody and the SEQ ID NO:1 polypeptide to which the antibody specifically. It is noted that

said molecules are organic and can provide the specific benefits of nutrition, but the nutritional benefit does not confer a specific utility to said molecules. Applicant further contends that the Furness declaration states that 2-D gels can be used to show differential expression in response to drugs and cytotoxic agents to evaluate their efficacy and toxicity. However, the examiner notes that the effect of the claimed antibody and the SEQ ID NO:1 polypeptide to which the antibody specifically binds in response to drugs and cytotoxic agents does not provide a specific utility to the claimed antibody and the SEQ ID NO:1 polypeptide to which the antibody specifically binds, because the focus is on the evaluating the drug and cytotoxic agent, and said evaluation is not dependent upon the specific utility of the claimed antibody and the SEQ ID NO:1 polypeptide to which the antibody specifically binds, but on generic properties thereof.

Applicant contends that objective evidence corroborates the utilities of the claimed invention, said utility being part of a database for expressed genes. However, being part of a database does not confer a specific function to the claimed antibody and the SEQ ID NO:1 polypeptide to which the antibody specifically binds, because the its specific utility is not validated.

Applicant further contends that rather than looking to the specific biological function or role of the claimed invention, the examiner should have looked first to the benefits it is alleged to provide. However, according to the revised written description guidelines, a sequence is required to have a specific and substantial and credible utility. As pointed out by Applicants the utility of a claimed DNA may have a specific and substantial utility because it hybridizes near a disease associated gene or it has gene regulating function. However, it is noted that the instant invention asserts neither of these utilities.

Applicant further contends that membership in a class of useful products can be proof of Utility, and that the examiner would require that all protease inhibitors possess a common utility. However the Examiner only requires that if the asserted utility is that of inhibiting protease, said assertion must be based on something other than a 40 % sequence homology to other protease inhibitors for the reasons stated above and of record. Applicant further contends that knowledge that GAPIP is a protease inhibitor is more than sufficient to make it useful for the diagnosis and treatment of cancer and immune cells. However, the knowledge that GAPIP is a protease has not been established and is a putative asserted function based on sequence homology.

Applicant contends that there is no authority for the proposition that the use as a tool for research is not a substantial utility. The examiner is not clear that said proposition was stated in the previous office action but notes that use in research is not a specific substantial utility for the claimed antibody and the SEQ ID NO:1 polypeptide to which the antibody specifically binds, according to the USPTO guidelines for written description. Applicant further contends that the Furness Declaration demonstrates that the claimed invention is a tool rather than an object of research and it demonstrates exactly how the tool is used. The examiner notes that its use as a tool is based on expression features and not a utility specific for itself. Applicant further contends that without the claimed invention it would be more difficult to generate information regarding the properties of tissues, cells, drug candidates and toxins apart form the additional

information about the polypeptide itself. However the Examiner notes the subjectivity of the phrase "more difficult", and that the use of the polypeptide encompassed by the instant claims as a tool, is not predicated on the specific utility of said polypeptide since any number of other antibodies and proteins could suffice in said tool, nor does said tool confer a specific utility to said polypeptide, nor to the antibodies which specifically bind said protein.

Applicant contends that mRNA levels are usually a good indicator of protein levels in a cell, with which the examiner agrees, and aggress with Applicant that the overwhelming majority of regulatory events occur at the initiation of transcription, but notes that this is not absolute as conveyed by Applicant. It is still noted by the examiner that no immunohistochemical evidence that the protein is actually expressed is disclosed in the specification.

Applicant asserts that the utility guidelines are inconsistent with the law. The examiner notes that as a patent examiner, these guidelines are followed in patent examination. Applicant contends that while throw away utilities lack a specific utility, general utilities do not. Applicant further contends that the training materials fail to distinguish between broad classes that convey information of practical utility and those that don't. However, it is the examiner's position that it would be hard to draw a line among broad classes that convey information of practical utility and those that don't because in a sense food is a practical utility and Applicant has categorized said utility for transgenic mice as a throw-away utility. It seems that the utility bar as described in the training guidelines is higher in the continuum of potential general utilities than Applicant contends is required under law.

Therefore, though Applicant's arguments have been carefully considered, they are not persuasive and the rejection is maintained, essentially for the reasons of record.

MAINTAINED Claims 3, 5-6, 8, 11-12, 14-17, and newly added claims 20-21, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Applicant traverses the rejection on the grounds that the office action appears to urge that every single member of the claimed genus of polypeptides and the antibodies that bind these fragments and variants must be specifically disclosed. However, the examiner makes no such claim.

Applicant traverses the rejection on the grounds that Applicants have provided the chemical structure of SEQ ID NO:1 and that there is no reliance merely on a description of functional properties of the claimed antibodies and the polypeptides to which they specifically bind.

It is noted by the examiner that though the claimed invention is directed to antibodies and the polypeptides to which they specifically bind, and not cDNA, the principle of the

following still holds for the genus of said antibodies and the polypeptides to which they specifically bind: a description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly&Co.*, 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

First the examiner notes that the disclosure of one species (SEQ ID NO:1) of a genus is not equivalent to a representative number of species. Second, it is noted by the examiner that the structural basis of the recited protease inhibitor activity or immunogenicity as recited for example in parts b and c, respectively, of claim 3 is not disclosed. Therefore, the disclosure of one amino acid sequence is not sufficient to provide adequate written description of the claimed genus of antibodies and the polypeptides to which they specifically bind.
Applicant contends that the present claims do not define a genus which is highly variant, as evidencd by Brenner's report that >40% identity over at least 70 residues is reliable in signifying homology between protein. However, the degree of variablitity is not an issue, but whether a genus with clearly defined boundries has been described. Applicant also contends that the art at the time of the present invention is further advanced that at the time of the Lilly and Fiers applications, and that with advances in molecular biology, and given the sequence information and additional detail provided by the application, that the present inventors were in possession of the claimed polypeptide variants and fragments at the time of filing of this application. However, written description is not based on what Applicants could do or invent, but what is actually described. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See Vas-Cath, page 1117.) Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Therefore, though Applicant's arguments have been carefully considered, they are not deemed persuasive, and the rejection is maintained essentially for the reasons of record.

MAINTAINED Claims 3, 5-6, 8, 11-12, 14-17, and newly added claims 20-21, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant traverses the rejection on the grounds that one skilled in the art need not make and test vast numbers of polypeptides that are based on the one amino acid sequence of SEQ ID NO:1, but that one need only screen a library or use PCR to identify relevant polynucleotides/polypeptides that already exist in nature, with which the examiner agrees.

Applicant contends that Brenner et al report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. However, the examiner notes that Brenner teaches homologies between domains and not between proteins, and that Brenner does not

specifically teach that structural homology is correlative with functional homology of the entire protein, and therefore the examiner disagrees with Applicant's contention that one would expect the recited SEQ ID NO:1 variants to have the functional activities of a growth associated protease, especially when it hasn't been established that SEQ ID NO:1 has such functions as outlined in the above utility rejection. These reasons counter Applicant's assertion that the examiner has failed to provide any reasons why one would doubt that the specification would enable one to make and use the recited antibodies which bind to the variants and fragments of SEQ ID NO:1.

However, applicants have not disclosed a naturally occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1, nor an antibody to a naturally occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1, other than SEQ ID NO:1 itself. Therefore, though Applicant's arguments have been carefully considered, they are not deemed persuasive, and the rejection is maintained essentially for the reasons of record. Therefore, though Applicant's arguments have been carefully considered, they are not deemed persuasive, and the rejection is maintained essentially for the reasons of record.

Conclusion

No Claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy M. DeCloux whose telephone number is 703 306-5821. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 703 308-3973. The fax phone numbers for the organization where this application or proceeding is assigned are 703 872-9306 for regular communications and 703 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308-0196.

Amy DeCloux, Ph.D.,
Patent Examiner,
March 4, 2003

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Primary Patent Examiner,
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